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10/747,686	12/30/2003	Mitchell S. Steiner	P-2769-US9	2903

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EXAMINER	
FUBARA, BLESSING M	

ART UNIT	PAPER NUMBER
1618	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/747,686	STEINER ET AL.	
	Examiner	Art Unit	
	Blessing M. Fubara	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 June 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,7-12 and 16-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,7-12 and 16-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/02/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Examiner acknowledges receipt of request for extension of time, amendment and remarks filed 6/12/07. Claims 4-6 and 13-15 are canceled. Claims 1-3, 7-12 and 16-32 are pending.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-3, 7-12 and 16-32 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is written description.

3. Claims 1-3, 7-12 and 16-32 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for toremifene, does not reasonably provide enablement for all compounds that are represented by formula I. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. This is scope of enablement

Scope of enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on

the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: 1) Nature of invention, 2) State of prior art, 3) The predictability or lack thereof in the art, 4) Amount of direction and guidance present, 5) The presence or absence of working Examples, 6) Breadth of the claims, and 7) Quantity of experimentation needed. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

Inhibiting pre-malignant lesions of prostate cancer in a human as it applies to prevention is addressed below.

1) Nature of the invention.

The nature of the invention is directed to methods of inhibiting the incidence of pre-malignant lesions of prostate cancer (intraepithelial neoplasia (PIN) and high grade prostate intraepithelial neoplasia (HGPIN) by administering a known drug to a human subject.

There is no one treatment, or combination of treatments, which provides inhibition (not occurring even the first time) of PIN/HGPIN. The best prevention, however, is a life-long commitment to physical activity, good nutrition, and normal prostate wellbeing. (See http://www.prostate-disorders.com/html/pin.php3), however, this is not prevention, as described in the article.

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher,* 427 F.2d 833, 166 USPQ 18

(CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statue. Further, their mode of action is often unknown or very unpredictable and administration of the drugs can be accompanied by undesirable side effects.

2) State of the prior art and the predictability or lack thereof in the art.

The state of the prior art is that it involves a myriad tests to determine the presence of PIN and to determine the stage of the PIN so that inhibiting or treating will include screening *in vitro* and *in vivo* to determine the effect of the compound on the specific disease state. There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face. The instant claimed invention is highly unpredictable as discussed below:

Thus, in the absence of a showing of correlation between all the conditions associated with **PIN** claimed as capable of being treated/prevented/suppress by the compounds of the instant claims, one of ordinary skill in the art is unable to fully predict possible results from the administration of the compounds due to the unpredictability of the role of predisposition and other latent factors and causes, for example.

3) Quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The quantity of experimentation needed is undue experimentation. One of ordinary skill in the art would first need to determine the type of conditions associated with **PIN, predisposition and other factors** and then determine when to administer the composition comprising the drug and also to the level needed to effectively prevent/suppress/treat the recurrence of PIN.

4) Level of predictability in the art.

The art pertaining to the treatment of all **PIN/HGPIN** remain highly unpredictable. As disclosed above, there is no absolute predictability even in view of the seemingly high level of skill in the art. Treatments for conditions associated PIN are normally tailored to the particular type of of mediator present, patient and patient compliance. There is no, and there can be no "magic bullet" against all conditions associated with PIN/HGPIN and other related conditions.

Therefore, the specification fails to provide sufficient support of the broad use of the compositions of the claims for inhibition of any PIN/HGPIN at any stage and in all cases necessitating one of ordinary skill in the art to perform an exhaustive search to determine what stage of the diseases can be treated/suppressed/prevented the instant claimed composition in order to practice the claimed invention.

In view of the lack of guidance, working examples, breadth of the claims, the level of skill in the art and state of the art at the time of the claimed invention was made, it would have required undue experimentation to make and/or use the invention as claimed.

It is noted that the specification must teach those of skill in the art how to make and how to use the invention as broadly claimed. In re Goodman, 29 USPQ2d at 2013 (Fed. Cir. 1994), citing In re Vaeck, 20 USPQ2d at 1445 (Fed. Cir. 1991).

The courts have stated that reasonable correlation must exist between scope of exclusive right to patent application and scope of enablement set forth in patent application. 27 USPQ2d 1662 *Ex parte Maizel.*

Scope of Enablement is considered in view of the Wands factors (MPEP 2164.01 (a)). In view of the quantity of experimentation necessary to determine the parameters listed above, the

lack of direction or guidance provided by the specification, the absence of working examples for the demonstration or correlation to the scope of the claimed invention.

A lack of adequate written description issue arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process. See, e.g., Fujikawa v. Wattanasin, 93 F.3d 1559, 1571, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996)

An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. See Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406.

A "representative number of species" means that the species, which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. The disclosure of only one species encompassed within a genus adequately describes a

claim directed to that genus only if the disclosure "indicates that the patentee has invented species sufficient to constitute the gen[us]."

In the present case, applicant claims metabolites/analogs of the triphenylethylene antiestrogenic compound depicted as formula (I) in claims 10 and 11. However, the specification merely mentions metabolites of the triphenylethylene antiestrogenic compound depicted as formula (I) without naming any of the metabolites. Secondly, the claims direct the use of the metabolites in formulation/dosage form for administration to a person for the claimed method. However, it is known that all metabolites are not all active, and metabolites can also be unstable. For example, DeGregorio in US 5,605,700 lists the following as metabolites of toremifene, one of the compounds that satisfies the generic compound of formula (I): **N-demethyltoremifene (4-chloro-1,2-diphenyl-[4-[2-(N-methylamino)ethoxy-]phenyl]-1-butene) or 4-hydroxytoremifene (4-chloro-1-(4-hydroxyphenyl)-2-phenyl-1-[4-[2-(N, N-dimethylamino)ethoyoxy]phenyl]-1-butene).** The specification does not say, ---metabolites of compound of formula (I) are .... In addition, there is no exemplification or description of dosage forms comprising/containing any metabolite of the compound of formula (I). It will thus require the artisan to carry out undue experimentation to determine those metabolites known or future identified metabolites to practice the full scope of the claimed invention. Furthermore, the listing in paragraph 67 of the published application that analogs and/or metabolites are 4-chloro-1,2-diphenyl-1-[4-[2-- (N-methylamino)ethoxy]phenyl]-1-butene; 4-chloro-1,2-diphenyl-1-[4-[2-(N,N- -diethylamino)ethoxy]phenyl]-1-butene; 4-chloro-1,2-diphenyl-1-[4(aminoeth-oxy)]-1-butene; 4-chloro-1-(4-hydroxyphenyl)-1-[4-[2-(N,N-dimethylamino)ethoxy]phenyl]-2-phenyl-1-butene; 4-chloro-1-(4-hydroxyphenyl)-1-[4-[2-(N-me- thylamino)ethoxy]phenyl]-2-

phenyl-1-butene; and 4-chloro-1,2-bis(4-hydroxy- phenyl)-1-[4-[2-(N,N-dimethylamino)ethoxy]phenyl]-1-butene is an invitation to experiment with these compounds since there is no clear description of what is an analog and what is a metabolite. Further, it is stated in paragraph 67 that the above listed compounds are derived upon administration of toremifene. Thus by the above listing, and applicant's admission that the analog/metabolite is not limited to the listed 5 compounds, it would require undue experimentation to practice the full scope of the claimed invention.

Therefore as discussed above, applicant has not provided a description of the structure of a representative number of compounds nor a description of the chemical and/or physical characteristics of a representative number of compounds nor a description of how to obtain a dosage form or compositions containing the representative number of specific compounds that are metabolites of the compound of formula (I) that would be administered to practice the claimed method. In other words, the Applicant has not described with sufficient clarity **metabolites of the compound of formula (I) suppressing or inhibiting the incidence of premalignant lesions of prostate cancer.**

The specification does not also provide distinction between analogs and metabolites.

The above rejection may be overcome by claiming the metabolites or analogs that are disclosed and described in the specification that is applicable in the claimed method. Further, toremifene is one of the compounds that have the generic formula (I).

What are the analog and the metabolites of the other compounds that have the general formula (I)?

Does the invention claims 10 and 11 use analogs or metabolites of the compound of formula (I)?

Claim 12 recites those same compounds listed in paragraph [0066] of the published application and identifies them as the compound while claims 10 and 11 specifically require the use of analogs and metabolites of the compound of the formula (I).

Response to Arguments

4. Applicant's arguments filed 6/12/07 have been fully considered but they are not persuasive.

A) Regarding claims 10 and 11, applicant argues that metabolites of toremifene are listed on page 18 paragraph 57 of the specification and that "it is not necessary for every species to be functional in order that claims to genus are considered."

B) Applicant argues that the skilled artisan would readily know how to prepare 60 mg composition of Toremifene, administer it to population of subjects, and determine the reduction of incidence of PIN/HGPIN in treated subjects, so that the claims meet the how to make and use prong of the written description.

Response:

Regarding claim 10 and 11, it is noted that toremifene is one of the compounds that formula I describes so that claiming metabolite of formula I encompasses drug compounds other than metabolites of toremifene. Secondly, since applicant admits that "it is not necessary for every species to be functional," it shows that all the metabolites of toremifene, and for that matter the metabolites of all the compounds that are described by formula I, cannot all reduce the

incidence of pre-malignant lesions of prostate cancer. it is thus suggested that applicant, in place of metabolite of compound of formula I, claim the metabolites of toremifene, using a Markush type language, that are listed and would reduce pre-malignant lesions of prostate cancer.

Regarding B), applicant's argument is noted as it regards to toremifene (chemically known as 4-chloro-1,2-diphenyl-1-[4-[2-(N,N-dimethylamino)ethoxy]phenyl]-1-butene) and as stated above, formula I describes drugs other than toremifene, for example, 4-chloro-1,2-diphenyl-1-[4-[2-- (N-methylamino) ethoxy]phenyl]-1-butene; 4-chloro- 1,2-diphenyl-1-[4-[2-(N- ,N-diethylamino) ethoxy]phenyl]-1-butene; 4-chloro-1,2-diphenyl-1-[4 (aminoethoxy)]-1-butene; 4-chloro-1-(4-hydroxyphenyl)-1-[4-[2-(N,N-dimeth- ylamino) ethoxy]phenyl]-2-phenyl-1-butene; 4-chloro-1-(4-hydroxyphenyl)-1-- [4-[2-(N-methylamino)ethoxy]phenyl]-2-phenyl-1-butene; and 4-chloro-1,2-bis(4-hydroxyphenyl)-1-[4-[2-(N,N-dimethylamino)ethoxy]pheny- l]-1-butene meet structure of formula I. Toremifene does not represent the full scope of formula I. Secondly, claim 1 is a method of reducing the incidence of pre-malignant lesions of prostate cancer and toremifene is administered to subjects having PIN, and what is observed and monitored is the percent of those having the PIN that progress to the stage of cancer. Thus there is not data showing reduction of PIN and how the reduction is monitored. One PIN is present, the study indicates that toremifene reduces the risk of cancer development. This is evidenced by the latest research on prostate cancer in the American Society of Clinical Oncology Annual meeting, May 15, 2005; and in the World Journal of Urology, May 21, 2003. Therefore, the specification does not enable the scope of the drugs that meet the limitations of formula I and the full scope of reducing the incidence of PIN. The enabled scope of the invention appears to be in the lowering of incidence of prostate cancer in subjects having PIN.

Double Patenting

5. Claims 1-3, 7-12 and 16-32 remain provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3, 7, 45 and 54-67 of copending Application No. 10/611,056. Although the conflicting claims are not identical, they are not patentably distinct from each other because the same compositions are employed in the examined claims and the copending claims to suppress/inhibit/reduce the incidence of premalignant lesions or PIN/HGPIN.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

6. Claims 1-3, 7-12 and 16remain are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-22 of copending Application No. 10/747,685. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claimed inventions are the same except that the examined application has analog in claims 10 and 11 and claims 1 and 2 of the co-pending application does not recite analog. However, later dependent claims 3-5 of the co-pending application 10/747,685 recite analog. The claims are not identical, but are inherently the same.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicant is reminded that there are several applications and issued patents that are subject to non-statutory obviousness double patenting rejections. It is therefore suggested to applicant to file all applicable terminal disclaimers or amend the claims to obviate any statutory double patenting in order to expedite prosecution and to avoid prosecutions in the applications rendered final in view of lack of appropriate actions from applicant.

No claim is allowed.

Response to Arguments

7. Applicant's arguments filed 6/12/07 have been fully considered but they are not persuasive.

Applicant request that the provisional obviousness type double patenting be held in abeyance until allowable subject matter is identified.

US 6,413,534: Applicant states that the use of 60 mg dose of formula I would not have been obvious;

US 6,413,533: Applicant states that the use of 60 mg dose of formula I would not have been obvious;

US 5,413,535: Applicant states that the use of 60 mg dose of formula I would not have been obvious;

US 6,410,043: Applicant states that the use of 60 mg dose of formula I would not have been obvious;

US 6,265,448: Applicant states that the use of 60 mg dose of formula I would not have been obvious;

US 6,632,447: Applicant states that the use of 60 mg dose of formula I would not have been obvious; and

US 6,899,888: Applicant states that the use of 60 mg dose of formula I would not have been obvious.

Response:

Since the claims are not found allowable, the provisional obviousness type rejection will continue to be made until the rejection is overcome.

Regarding the issued patents US 6,413,534; US 6,413,533; US 5,413,535; US 6,410,043; US 6,265,448; US 6,632,447 and US 6,899,888 and the 60 mg administered, it would have been prima facie obvious to use amount of toremifene/formula I that would be effective to reduce the risk of the incidence of developing prostate cancer in subjects having PIN.

No claim is allowed.

8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Blessing M. Fubara whose telephone number is (571) 272-0594. The examiner can normally be reached on 7 a.m. to 5:30 p.m. (Monday to Thursday).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Hartley can be reached on (571) 272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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